REMARKS

Claims 2-4, 6 and 17-20 are present in this case. Claims 1, 5 and 7 of the originally presented claims have been canceled and new claims 19 and 20 substituted therefor.

The invention lies in the finding that prodrugs comprising a carrier moiety selected from cinnamoyl, benzoyl, phenylactyl, 3,4-methylenedioxycinnamoyl and 3,4,5-trimethoxycinnamoyl, chemically linked to a therapeutic polypeptide aa_n , wherein aa is an amino acid and n is an integer from 2 to 10 through a non-therapeutic linker species, i.e., an amino acid, wherein the therapeutic polypeptide is substantially non-absorbed following oral administration, can be orally administered to provide effective therapeutic levels.

The rejection of the claims under 35 U.S.C. 112, second paragraph has been mooted by the above proffered amendment.

The provisional rejection based on obviousness/double patenting with respect to copending application No. 10/237,254 has been avoided by submission herewith of a terminal disclaimer.

The Examiner has rejected claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Johansen.

Johansen is specific to the preparation of peptides based on a reaction of a so-called substrate component also called acid component or donor, and containing the moiety A with a so-called amine component, also called nucleophile component or acceptor, and containing the moiety B thereby to form a peptide A–B. The polypeptides which can be produced by the Johansen reaction are enkephalins, somatostatin, somatostatin analogs and peptides with similar biological activities, and the so-called "sleep peptide" (Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu). The patentee states that in order to improve the solubility characteristics of the peptides formed, to use as the N-terminal amino acid arginine or another ionizable amino acid during the synthesis steps

and then cleave the arginine from the peptide with a specific enzyme e.g. trypsin, when the desired amino acid sequence is otherwise in order.

First it is noted that the Johansen patent does not disclose or describe the prodrugs or compositions of the invention since there is no disclosure of the tripartite structure of polypeptide, carrier and linker species of the invention. Further there is no teaching of this structure allowing for the oral administration of drugs otherwise unavailable for this form of administration. The Johansen peptides do not teach or suggest the polypeptides of the invention having a tripartite structure of therapeutic polypeptide aa_n, the non-therapeutic binder species and the carrier moiety as now claimed.

The Examiner's rejection of claims 1-7, 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Goldstein in view of Bundgaard is no longer well taken in view of the amendments made to the claims.

Goldstein is directed to providing improved polypeptide analgesics having opioid activity and particularly enkephalins. Goldstein teaches that this can be accomplished through novel oligopeptides provided with alternating basic hydrophilic amino acids and hydrophobic amino acids, having at least five units which oligopeptides are employed as precursors for conjugating to opioid compounds, particularly polypeptide opiods. The oligopeptides are joined by a short chain to a phenolic group, which may be part of a tyrosyl unit or a morphine alkaloid or synthetic mimetic analogs thereof.

As acknowledged by the Examiner Goldstein fails to teach the carrier moiety, a critical element of the instant invention.

To cure this defect, the Examiner relies on Bundgaard cited as teaching "methods for preparing the prodrug form of allopurinol and thereby to provide improved aqueous solubility and oral administration as compared to the parent compound... and teaches that acyl groups such as benzoyl and cinnamoyl are well known carrier moieties." The Examiner has, based on her interpretation of the references concluded that it would be obvious (35 U.S.C. 103) to have modified the opioid of Goldstein by linking with acyl

groups such as cinnamoyl or benzoyl because of the expectation of successfully producing a prodrug of met-enkephalin for improved solubility and oral administration.

First the combination of Goldstein and Bundgaard does not teach the basic inventive concept of a prodrug comprising a carrier moiety linked through a non-therapeutic linker species to a therapeutic polypeptide, which represents the invention as herein claimed.

Second, Bundgaard discloses as specific examples of compounds of formula Ia or I'a (see Detailed Description of the Invention – column 7, line 55 – column 8, line 47) some 128 named compounds. In listing the "still more preferred compounds" (columns 12-13 and "Ever more preferred compounds" (columns 13-14) etc., neither benzoyl or cinnamoyl are included in any of the preferred listings. The lists constitute a shot gun disclosure, in fact deemphasizing the use of cinnamoyl and benzoyl.

The drug involved allopurinol in Bundgaard is not comparable to the therapeutic polypeptide of the invention. Furthermore allopurinol has a solubility in water as mg/ml at 25° of 0.48 (Merch Index Tenth Edition) and still further the drugs of Bundgaard are administered "via rectal, oral or parenteral dosage forms" (column 14, lines 55 et seq., see also the Abstract).

It is submitted that there is nothing in Bundgaard which would cause the artisan to select either benzoyl or cinnamoyl and to combine it with the teaching of Goldstein.

The Examiner's rejection is based on hindsight, an improper conclusion that an invention is unpatentable because "obvious," by reading back into the prior art the teachings of the invention which came later.

Knowing the invention makes it seem obvious. Thus the U.S. Supreme Court has cautioned against "slipping into the use of hindsight" and urged courts "to resist the temptation to read into the prior art the teachings of the invention in issue." *Graham v. John Deere Co.*, 383 U.S. 1, 36, 148 USPQ 459, 474 (1966). For example, impermissible "hindsight" is using knowledge of the solution to determine that the answer to the technical problem was "obvious," whereas to one without knowledge of the solution, the

answer was not "obvious" at all. It is an impermissible use of hindsight to combine pieces of the prior art to argue that a combination invention is obvious. There must be something in the prior art that suggested the combination of these particular prior art devices and processes other than the hindsight gained from knowing that the inventor chose to combine these particular things in this particular way. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988).

In addition to the improper use of hindsight, the Examiner has used the test of "obvious to try." The Court of Appeals for the Federal Circuit has held that "obvious to try" is not the proper test to apply in using the criterion of obviousness of Patent Code § 103.

In view of the proffered amendments and the presented arguments and the enclosed disclaimer, it is submitted that the application is now in condition for allowance and notification to this effect is respectfully requested.

Respectfully submitted,

By: _____

Evelyn M. Sommer, Reg. No. 19,603
McCarter & English
City Place I
185 Asylum Street
Hartford, CT 06103-3495
Tele: (203) 324-1800
Fax: (203) 323-6513

HARTFORD: 604075.01